An update of a systematic review and meta-analyses exploring flavours in intervention studies of e-cigarettes for smoking cessation

Running title: E-cigarette flavours review update

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Key words

Smoking cessation; e-cigarettes; flavours; tobacco; nicotine; systematic review

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**ABSTRACT**

**Aims**

To determine patterns of e-cigarette flavour use (sweet, tobacco, menthol/mint) in interventional studies of e-cigarettes for stopping smoking, and to estimate associations between flavours and smoking/vaping outcomes.

**Methods**

Update of secondary data analyses, including meta-analyses subgrouped by flavour provision and narrative syntheses, incorporating data from January 2004 to February 2024. Eligible studies were identified from a Cochrane review. Studies provided adults who smoked cigarettes with nicotine-containing e-cigarettes for smoking cessation and provided data on e-cigarette e-liquid flavour use. Outcomes included participants’ flavour use measured at any time, plus smoking abstinence, abstinence from all tobacco or commercial nicotine products, and allocated product use at 6 months or longer, reported as risk ratios with 95% confidence intervals. We assessed risk of bias using the Cochrane Risk of Bias 1 tool.

**Results**

We included 25 studies (n=16,748); 21 contributed to subgroup meta-analyses and 18 provided flavour choices. We judged 15 studies at high, seven at low, and three at unclear risk of bias. In studies where participants had a choice of flavours, some switching between flavours occurred (five studies). A preference for sweet (including fruit) flavours over tobacco and menthol was indicated (in 6 of 11 studies); however, there were differences across studies. Subgroup meta-analyses showed no clear associations between e-liquid flavours provided and smoking cessation or study product use. One included study randomised participants to two different flavour conditions and found similar cessation rates and long-term e-cigarette use between arms at 12 months.

**Conclusions**

Some people using e-cigarettes to quit smoking switch between e-cigarette flavours during a quit attempt. Sweet flavours may be preferred overall, but this may differ depending on context. Based on intervention studies there is no clear association between the use of e-cigarette flavours and smoking cessation or longer-term e-cigarette use, possibly due to a paucity of data.

**BACKGROUND**

The 2024 update of the Cochrane living systematic review of e-cigarettes (EC) for smoking cessation found that EC can help people stop smoking combustible cigarettes.(1) Nicotine e-liquids are available in many flavours. However, evidence on whether and how flavours influence the effectiveness of EC is limited.(2) Although EC are less harmful than combustible cigarettes they are not risk-free, and there have been debates around flavour restrictions as a way to minimise youth vaping.(3) Additionally, concerns persist regarding the impact of regulating flavours on the appeal, use and effectiveness of EC as a stop-smoking tool.(3)

Observational data from the US has found fruit to be the most popular e-liquid flavours and that people are more likely to successfully transition away from smoking if they use non-tobacco flavoured EC.(4, 5) However, this data needs to be triangulated in randomized controlled trials (RCTs).

In 2022, we published secondary syntheses of intervention studies included in the Cochrane living review discussed above.(6) We incorporated 16 studies identified up to January 2022. None directly compared different flavours between randomised groups and there was no clear evidence that e-liquid flavours affected smoking or vaping at 6 months or longer. There was also no clear evidence of the popularity of particular e-liquid flavours over others. The limited nature of the data synthesised hampered our ability to draw clear conclusions. We set out to update these analyses to incorporate the most recent data and to continue to inform flavour policy discussions.

**METHODS**

This paper updates an earlier version of this review.(6) We present a summary of the key methods and findings, with a particular focus on content added since the last version. For a more detailed version of this review see Supplemental File 1. We pre-specified our methods: <https://osf.io/HPBYW/>.

**Objectives**

1. To investigate patterns of EC flavour use (sweet, tobacco, menthol/mint) where participants were provided with a choice of flavours;
2. To investigate whether the effectiveness of using nicotine EC to stop smoking was associated with flavour of EC used;
3. To investigate whether the long-term (6 months or longer) use of the allocated study product was associated with flavour of nicotine EC used.

**Searches, screening, and data extraction**

We identified eligible studies from our Cochrane review (i.e., intervention studies in which people who smoked combustible cigarettes were provided with or asked to use EC, published from 2004) up to February 2024.(1) To be included here, studies had to report information on e-liquid flavour use and report at least one of the following outcomes at six months or longer: 1) combustible cigarette abstinence; 2) use of study product (EC or comparator intervention). Eligibility for the Cochrane review was determined in duplicate, whereas a single reviewer determined eligibility for this review.

We used relevant data previously extracted in duplicate for the Cochrane review along with new data gathered for this review,(1) including an additional outcome: participants abstinent from all tobacco or commercial nicotine products (excluding medicinal nicotine replacement therapy, and including EC) at 6 months follow-up or longer. Additional data was extracted by one reviewer and verified by another. We categorised e-liquid flavours as: tobacco only; menthol/mint only; sweet only (including fruit, candy and dessert flavours); unflavoured only; choice of tobacco or menthol/mint; choice of tobacco, menthol/mint or sweet.

We applied risk of bias judgements from the Cochrane review, which were conducted in duplicate using the Cochrane risk of bias 1 tool.(1) Studies were deemed low, unclear or high risk of bias overall.

**Syntheses**

When studies offered participants a range of flavours, we extracted this information and reported it narratively. To investigate associations between flavours and our outcomes of interest, we subgrouped our existing Cochrane meta-analyses by the e-liquid flavour(s) provided in the studies. We conducted analyses using RevMan 5.4, using I2 to assess subgroup differences. An I2 greater than 50% was deemed substantial and potentially indicative of an association between flavours and the outcome of interest. Pooled subgroup effects were calculated using random effects analyses and presented as risk ratios (RR) with 95% confidence intervals (CI). We extracted results of any within-study analyses by flavours allocated/chosen in the studies and synthesised them descriptively.

**RESULTS**

Of the 90 studies identified in our Cochrane review to February 2024, 25 were eligible for this review; nine of these new to this review (see Table 1 and supplemental file 1). Of the 25, 21 were randomised controlled trials (RCTs) included in subgrouped meta-analyses, and 18 reported providing participants with a choice of flavours (some studies qualified for both categories). Fifteen studies were judged to be at high risk of bias, three at unclear risk and seven at low risk. One study randomised participants to different e-liquid flavours (tobacco only e-liquids versus choice of sweet, menthol/mint or tobacco flavour e-liquids) and reported on smoking cessation and long-term product use.

**Studies offering a choice of flavours**

Of the 18 studies offering a choice of flavours, four provided participants with a choice of tobacco or menthol/mint flavours, one with a choice of sweet or tobacco flavours and the remaining studies provided a choice of sweet, menthol/mint or tobacco flavours. Eleven provided a breakdown of flavours used. Six (US and UK based) showed sweet flavours were more popular than menthol/mint and tobacco flavours (Begh 2021, Dawkins 2020, Hajek 2019, Myers Smith 2022, Price 2022, Xu 2023; Table 1). One Swiss study found 75% of participants preferred sweet and menthol/mint flavours (no further breakdown) over tobacco.(7) Two studies based in Italy showed over 80% of participants preferred tobacco flavour versus other flavours offered.(8, 9) One UK study found no clear preference between sweet, tobacco, and mint/menthol flavours,(10) whilst a US study that recruited Latinx and African-American participants reported 54% chose menthol/mint, 17.6% tobacco, and 28% sweet flavours.(11) Xu 2023 found that participants preferred sweet flavours overall, but that menthol/mint e-liquid was most popular among those who usually smoked menthol cigarettes, while tobacco and sweet flavours were the most popular among those who usually smoked non-menthol cigarettes.(12)

Figure 1 (new to this update) summarises flavour use over time in five studies that provided flavour use information at multiple time points and offered a choice of tobacco, menthol/mint and sweet EC flavours. This data is provided for descriptive purposes only (it has not been meta-analysed) and cannot account for differences in the characteristics of included studies or participants. Although tobacco flavour was most used at the earliest time point, this appeared to decline substantially at later time points, whereas use of menthol remained fairly stable between zero and six/eight months, and use of sweet flavours increased slightly in the same period.

Using individual participant data from two studies, we mapped flavour switching behaviour (Figure 2).(11, 12) In both studies the majority of people stayed with their initial flavour choice throughout; however, a substantial minority switched between flavours over time. Pulvers 2020 (included in previous update) found a slight decrease in menthol use and an increase in fruit flavours, with stable tobacco flavour use.(11) Xu 2023 (new to this update) found a slight increase in menthol/mint use, while the use of sweet and tobacco flavours stayed consistent.(12)

**Associations between flavours and outcomes**

One study, new to this update and conducted by an EC company, randomised participants into three groups. Two groups were relevant when comparing flavours – tobacco flavoured e-liquid versus choice of sweet, tobacco or menthol e-liquids.(12) The study reported similar 12-month, 30-day point prevalence quit rates in the tobacco (51/285; 17.9%) and flavour choice (40/281; 14.2%) groups. At 12-month follow-up, 83/261 (31.8%) participants in the tobacco group had used an EC in the last 30 days versus 91/261 (34.9%) in the flavour choice group.

No clear evidence emerged from our subgrouped meta-analyses (21 studies across analyses) that flavour moderated smoking abstinence or long-term product use. The I2 for subgroup differences suggested substantial statistical heterogeneity (65.2%) for the comparison ‘Nicotine EC versus NRT’ and long-term study product use outcome (5 studies; Figure 3). However, substantial within subgroup statistical heterogeneity was also detected and all subgroup analyses were limited by imprecision. Only one study measured abstinence from both combustible cigarettes and EC across study arms.(13) This was a small study with small numbers of participants quitting. Of the two participants abstinent at 8 months in the EC intervention arm both were using sweet flavours (as opposed to menthol or tobacco flavours) early in the study. No participants quit in the standard care arm.

Five studies that provided participants with a choice of flavours supplied data on the flavour choices of participants who quit smoking versus those who did not achieve abstinence. No definitive patterns of flavour use emerged.

**DISCUSSION**

This update builds on a previous systematic review investigating the role of e-liquid flavours in people who smoked.(6) It extends the ongoing Cochrane living review of EC for smoking cessation.(1)

The previous version of the review was largely inconclusive, revealing no specific e-liquid flavour preferences across studies nor a clear association between EC flavours and smoking abstinence or longer-term EC use.(6) However, there was limited evidence of some people switching e-liquid flavours during a quit attempt. Overall, there was substantial uncertainty in our findings. This update incorporates nine additional studies, bringing the total to 25. One was a new RCT directly comparing two flavour conditions.(12) There was no clear evidence to suggest that particular flavours were associated with better quit rates or greater long-term use of EC. At this update most studies providing information on flavour use provided evidence that sweet flavours were preferred; however, there were some notable exceptions. Two Italian studies found tobacco flavour e-liquids were preferred over other flavours,(8, 9) and two studies found evidence that people who had a previous history of smoking mentholated combustible cigarettes were more likely to prefer menthol flavoured e-liquids.(11, 12) One of the studies was carried out in Latinx and African‐American participants who more commonly smoke menthol cigarettes than the remaining US population.(14) Therefore, there may be cultural differences in e-liquid flavour use that need to be considered. In addition, there is now increased evidence that although some people continue using the same e-liquid flavour throughout a quit attempt, there are also numerous people who switch between flavours, with the most common switching being away from tobacco to other flavours.

The primary outcome of this review was abstinence from combustible cigarettes, but several other outcomes, including abstinence from both combustible cigarettes and EC, warrant reporting in future studies. For this update we investigated this as an additional outcome, as quitting all products is the ultimate aim in order to achieve the maximum health benefit. However, only one of our included studies measured this across all participants in the study.(13) Due to the small sample size and limited cessation rate in this study, the findings for this outcome were inconclusive. Future studies investigating EC in people who smoke should also collect detailed information on flavour use over time and investigate any potential moderating effects on study outcomes. Ideally more RCTs should be carried out randomising participants to differing flavour conditions as this is the only study design that can be used to establish causality. This is vital as regulation of EC flavours should take into account both the role of flavours in achieving smoking abstinence and the uptake of EC in young people who have not previously smoked, to balance risks and benefits.

Our approach is based on established systematic review methods, with thorough search, study selection and data collection methods.(1) For reasons of pragmatism screening for this review was carried out by a single reviewer. However, as initial eligibility was determined in duplicate for the Cochrane review and eligibility for this review relied on the reporting of outcomes extracted in duplicate for the Cochrane review, this is deemed to be a minimal risk. There are uncertainties in our conclusions due to the limited data available. Although other studies have also indicated preferences for sweet flavoured e-liquids over other flavours,(4, 15) further research could change conclusions, underscoring the need for continuous monitoring of emerging data.

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*Table 1: Characteristics of included studies*

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Device type** | **Total N baseline** | **Flavours provided** | **Comparison (C) or single arm (S)** | **Study design** | **Length of follow-up (months)** | **Overall risk of bias judgement** | **Country** | **Population characteristics** |
| Auer 2024\* | Refillable | 1246 | Choice of sweet, tobacco or menthol | C (EC vs counselling) | RCT | 6 | High | Switzerland | People who smoke combustible cigarettes |
| Begh 2021 | Refillable | 325 | Choice of sweet, tobacco or menthol | C (EC vs standard care) | RCT | 8 | High | UK | People who smoke combustible cigarettes with no plans to stop |
| Bullen 2013 | Cig-a-like | 657 | Tobacco only | C (EC vs nicotine patches vs placebo EC) | RCT | 6 | Low | New Zealand | People who smoke combustible cigarettes and willing to quit |
| Caponnetto 2013 | Cig-a-like | 300 | Tobacco only | C (EC vs lower nicotine EC vs non-nicotine EC) | RCT | 12 | Unclear | Italy | People who smoke combustible cigarettes |
| Caponnetto 2023\* | Refillable | 220 | Choice of tobacco or menthol | C (EC vs heated tobacco) | RCT | 6 | High | Italy | People who smoke combustible cigarettes |
| Carpenter 2023\* | Pod | 638 | Choice of sweet, tobacco or menthol | C (EC vs no intervention) | RCT | 6 | High | USA | People who smoke combustible cigarettes |
| Cobb 2021 | Cartridge | 520 | Choice of tobacco or menthol | C (EC nicotine 2 strengths; non-nicotine EC; cigarette substitute) | RCT | 6 | Low | USA | People who smoke combustible cigarettes |
| Dawkins 2020 | Refillable | 80 | Choice of sweet, tobacco or menthol | C (EC vs UC) | Prospective cohort | 6 | High | UK | People who smoke combustible cigarettes. Recruitment at homeless centres |
| Eisenberg 2020 | Cig-a-like | 376 | Tobacco only | C (EC + counselling vs non-nicotine EC + counselling vs counselling only) | RCT | 6 | Low | Canada | People who smoke combustible cigarettes and motivated to quit |
| Ely 2013 | Cig-a-like | 48 | Choice of sweet, tobacco or menthol | S (All used EC) | Prospective cohort | 6 | High | USA | People who want to quit combustible cigarettes or switch to EC |
| Hajek 2019\* | Refillable | 886 | Tobacco only | C (EC vs NRT) | RCT | 12 | Low | UK | People who smoke combustible cigarettes |
| Hajek 2022 | Refillable | 1140 | Choice of sweet or tobacco | C (EC vs NRT) | RCT | 6 | Low | UK | People who smoke combustible cigarettes, 12-24 weeks pregnant |
| Halpern 2018 | Cig-a-like | 6006 | Choice of sweet, tobacco or menthol | C (Usual care (UC); UC +EC; UC+EC+ NRT + bupropion or varenicline; UC+EC+ NRT + bupropion or varenicline + incentives; as before plus financial incentive) | RCT | 12 | High | USA | People who smoke and employees and their spouses that used Vitality wellness programs |
| Holliday 2019 | Refillable | 80 | Choice of sweet, tobacco, mint/menthol, or unflavoured | C (EC vs no intervention) | RCT | 6 | High | UK | People who smoke combustible cigarettes with peridontis |
| Klonizakis 2022\* | Cartridge | 248 | Choice of tobacco or menthol | C (EC vs non-nicotine EC; EC vs NRT) | RCT | 6 | Unclear | UK | People who smoke combustible cigarettes |
| Lee 2018 | Cig-a-like | 30 | Tobacco only | C (EC vs nicotine patches) | RCT | 6 | Low | USA | People who smoke and presented to the anesthesia preoperative clinic for elective surgery 3 or more days before surgery |
| Lucchiari 2020 | Cig-a-like | 210 | Tobacco only | C (nicotine EC vs non-nicotine EC) | RCT | 12 but data only available at 6 | High | Italy | Participants are 55 years or more and have smoked at least 10 combustible cigarettes a day for the past 10 years |
| Myers Smith 2022 | Refillable | 135 | Choice of sweet, tobacco or menthol | C (EC vs NRT) | RCT | 6 | Low | UK | People who smoke combustible cigarettes and find quitting difficult |
| Polosa 2015 | Refillable | 71 | Choice of sweet, tobacco or menthol | S (All used EC) | Prospective cohort | 12 | High | Italy | People who smoke combustible cigarettes, making first purchase at vape shop |
| Pope 2024\* | Pod | 972 | Choice of sweet, tobacco or menthol | C (EC vs UC) | RCT | 6 | High | UK | People attending the Emergency Department who smoked tobacco daily |
| Pratt 2022\* | Cartridge | 240 | Choice of tobacco or menthol | C (EC vs no intervention) | RCT | 6 | High | USA | People who smoke combustible cigarettes with serious mental illness |
| Price 2022\* | Refillable | 871 | Choice of sweet, tobacco or menthol | S (All offered EC) | Single-arm intervention study | 12 | High | UK | People who smoke combustible cigarettes from lower socioeconomic groups |
| Pulvers 2020 | Pod | 186 | Choice of sweet, tobacco or menthol | C (EC versus no intervention) | RCT | 6 | High | USA | African American and Latinx people who smoke combustible cigarettes |
| Russell 2021 | Pod | 426 | Choice of sweet, tobacco or menthol | C (NRT; EC with nicotine salt e‐liquid pods; EC with freebase nicotine e‐liquid pods) | RCT | 6 | Unclear | UK | People who smoke combustible cigarettes |
| Xu 2023\* | Pod | 837 | 1. Tobacco only;
2. Choice of sweet, tobacco or menthol
 | C (Tobacco flavour EC vs choice of flavour EC vs quit advice) | RCT | 12 | High | USA | People who smoke combustible cigarettes |

Footnote: Refer to supplemental file 1 for included study references. EC = electronic cigarettes; NRT = nicotine replacement therapy; RCT = randomised controlled trial; UC = usual care; \*new to this update

*Figure 1. Flavour choice over time in five studies providing options including tobacco, mint/menthol and sweet flavours*

Figure 2. EC flavour use over time among participants in a) Pulvers 2020,(11) b) Xu 2023.(12) Arrows illustrate the flow of flavour choice and switching behaviour (only including participants that provided data at follow-up points)

Footnote: a) at baseline and 6-week follow-up participants were provided with mango, mint, menthol or tobacco flavours. At 6-month follow-up participants were self-sourcing flavours and so additional flavours were being used, as specified; b) up to 6 months participants were supplied with tobacco, mint, menthol, mango, creme, fruit or cucumber by the study; at 12 months participants were self-sourcing EC supplies

*Figure 3. Study product use at 6 months or longer, EC versus NRT*

Footnote: EC = electronic cigarettes; FBNP = free base nicotine pods; NSP = nicotine salt pods; NRT = nicotine replacement therapy